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13. ABSTRACT (Maximum 200 Words) The promise of research into breast cancer genetics is that it will provide us with new insights into the etiology of breast cancer that can be translated to strategies for early diagnosis and treatment for the larger population of women who develop breast cancer without having a genetic predisposition. An academic award represents an outstanding opportunity for me to critically appraise the emerging role of genetics in clinical breast cancer care and forge new avenues of research. Toward this goal, I plan to accomplish the following during the award period: 1) perform a thorough review of the cytogenetic and molecular genetics literature to identify potential chromosomal regions that may harbor genes whose abnormal function is critically involved in the development of breast cancer. 2) develop a robust panel of markers that can be used for clinical correlative studies of hereditary breast cancers. 3) develop a tissue repository composed of biological specimens from 500 patients with inherited breast cancer (e.g fresh frozen tumor specimens, or paraffin embedded tumor specimens and normal blood lymphocytes, DNA and sera whenever possible). These studies will lead to an improved understanding of the biology of breast cancer which will ultimately translate into more effective therapies.			
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## INTRODUCTION

As a physician-scientist, I have had extensive training in clinical oncology and in molecular biology and genetics; I am ideally positioned to bridge the gap between the two. The academic award has represented an outstanding opportunity for me to critically appraise the emerging role of genetics in clinical breast cancer care and forge new avenues of research. Toward this goal, I plan to accomplish the following during the period of my academic award.

1) perform a thorough review of the cytogenetic and molecular genetics literature to identify potential chromosomal regions that may harbor genes whose abnormal function is critically involved in the development of breast cancer.

2) develop a robust panel of markers that can be used for clinical correlative studies of hereditary breast cancers.

3) develop a tissue repository composed of biological specimens from 500 patients with inherited breast cancer (e.g. fresh frozen tumor specimens, or paraffin embedded tumor specimens and normal blood lymphocytes, DNA and sera whenever possible).

Using these unique resources, my future studies will characterize the molecular pathways which allow a normal breast cell to become cancerous in individuals who are genetically predisposed. I will also develop longitudinal follow up studies to correlate clinical outcomes with molecular characterization and epidemiologic risk factors. These studies will no doubt lead to an improved understanding of the biology of breast cancer which will ultimately translate into more effective therapies.

### **Task I**

**perform a thorough review of the cytogenetic and molecular genetics literature to identify potential chromosomal regions that may harbor genes whose abnormal function is critically involved in the development of breast cancer.**

This year we published two reviews on the genetics of breast cancer. In the next year, we are completing two manuscripts which will focus on the chromosomal abnormalities and genetic alterations in breast cancer.

#### Publications

**Olopade OI, Pichert G.** Cancer genetics in oncology practice. Ann Oncol 2001 Jul;12(7):895-908

**White, M Olopade OI.** Cancer Risk Assessment: Toward a primary prevention of breast and ovarian cancers. Oncology Economics 2000; 1(11):40-45.

### **Task II**

**develop a robust panel of markers that can be used for clinical correlative studies of hereditary breast cancers.**

We have developed several probes for fluorescent in situ hybridization and have begun to apply these probes to a panel of breast tumors in our tumor bank.

Breast cancer is a heterogenous disease caused by the progressive accumulation of genetic changes in a growing number of oncogenes and tumor suppressor genes. Germ-line mutations in the *BRCA1* tumor suppressor gene result in breast cancers characterized by young age of onset, estrogen receptor negativity (ER-), and distinctly high grade tumor phenotype. The secondary genetic changes required for tumor development in *BRCA1* carriers are largely unknown. Somatic amplification of *HER2/neu*, a neighboring gene to *BRCA1* on 17q, is also associated with aggressive high grade, (ER-) breast tumors. C-MYC interacts with the *BRCA1* protein, and the gene is amplified in 5-50% of breast cancers. We have assessed the relative

contributions of *HER-2/neu* and/or *C-MYC* amplification to the aggressive biology of *BRCA1*-associated tumors.

We performed FISH using the PathVysion™ *HER-2* and *C-MYC* assays on formalin-fixed paraffin-embedded tumor tissues from women with known deleterious *BRCA1* mutations. *HER-2/CEP17* and *C-MYC/CEP8* ratios were scored and compared with clinico-pathological data and immunohistochemical studies. With more than 98 primary breast tumors and cell lines examined by FISH, we are yet to find a single *BRCA1*-associated tumor with high levels of *HER2/neu* gene amplification (n=53). In contrast, 6/41 (15%) sporadic tumors demonstrated *HER-2/CEP17* ratio  $\geq 5$  (p=0.048). To date, we have observed *C-MYC/CEP8* ratio  $\geq 2$  in 10/16 (62%) *BRCA1* tumors including 4 tumors with ratios  $\geq 4$ . Our data suggest that a germ-line mutation in the *BRCA1* gene inhibits the ability of somatic cells to highly amplify the adjacent *HER-2/neu* oncogene but *C-MYC* amplification occurs in a significant proportion of *BRCA1* tumors. Thus, it is likely that *BRCA1* and *HER-2/neu* associated tumors progress through distinct molecular pathways.

#### Publications

A Blackwood, H Yang, K Nathanson, M Stratton, D Easton, K Calzone, J Stopfer, **O Olopade**, S Cummings, A Ganguly, J Berlin, and B Weber. Predicted probability of breast cancer susceptibility gene mutations. Submitted to San Antonio Breast Conference 2001.

**Olopade OI**, Grushko T, Hagos F, Adeyanju M, Adams, A, Blackwood-Chirchir A, Weber B and Perou C. Dissection of cooperating genetic pathways involved in aggressive early onset breast cancer reveals mutually distinct roles for *BRCA1* and *HER2/neu* genes. Submitted to San Antonio Breast Conference 2001.

#### Task III

**develop a tissue repository composed of biological specimens from 500 patients with familial or hereditary breast cancer (e.g fresh frozen tumor specimens, or paraffin embedded tumor specimens and normal blood lymphocytes, DNA and sera whenever possible).**

We have developed a clinical protocol for the tumor bank. The protocol has not yet been approved by the DOD Human Subjects Review Panel. Hence we have not enrolled any patients specifically to this study. However, we have identified collaborators and other sources of tumor materials that will be ready and available for recruitment once our study is approved.

#### KEY RESEARCH ACCOMPLISHMENTS:

Too early to report

#### REPORTABLE OUTCOMES:

Academic Productivity in 2001.

1. Fackenthal JD, Marsh DJ, Richardson A, Cummings SA, Eng C, Robinson BG, **Olopade OI**. Male breast cancer in Cowden Syndrome patients with germline *PTEN* mutations. *J Med Genet* 38: 159-164, 2001.
2. \*Eisenbeis CF, Winn D, Poelman S, Polsky CV, Rubenstein JH, **Olopade OI**: A case of pulmonary toxicity associated with G-CSF and doxorubicin administration Ann Hematol 80:121-123,2001.
3. **Olopade OI**, Grushko T Gene expression profile of hereditary breast cancer N Engl J Med.. 344:2028-2029, 2001.

4. Runnebaum IB., Wang-Gohrke S, Vesprini D, Kreienberg R, Lynch H, Moslehi R, Ghadirian P, Weber B, Godwin AK, Risch H, Garber J, Lerman C, **Olopade OI**, Foulke WD, Karlan B, Warner E, Rosen B, Rebbeck T, Tonin P, Dubé M, Kieback D G, SA Narod. Progesterone receptor variant increases ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers who were never exposed to oral contraceptives *Pharmacogenetics*. 7:635-638, 2001.
5. \*Stadler WM, Steiberg G, yang X, Hagos F, Turner, C, **Olopade OI**. Alterations of the 9p21 and 9q33 chromosomal bands in clinical bladder specimens by fluorescent-in-situ-hybridization. *Clinical Cancer Research* 6:1676-82, 2001.
6. \*Grushko T. A., Blackwood-Chirchir A, Schumm P, F. Hagos, Le Beau M, Weber, B, **Olopade OI**. Her2/neu gene amplification is not a feature of *BRCA1*- associated breast cancer progression. (*Cancer Research* In press)

**CONCLUSIONS:**

N/A Too early

**REFERENCES:**

N/A

**APPENDICES:**

N/A